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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/786,400	02/24/2004	Alexander William Oxford	56476-DIV2 (71661)	2879

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EXAMINER	
TRUONG, TAMTHOM NGO	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 08/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/786,400	OXFORD ET AL.	
	Examiner	Art Unit	
	Tamthom N. Truong	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4-3-06 (RCE)*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-48 and 51-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-48 and 51-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4-3-06 has been entered.

Claims 1-42, 49 and 50 have been cancelled.

Claims 43-48 and 51-57 are pending.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 43, 46-48 and 51-54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

a. Claims 43 recites: "*A method for the acute or prophylactic treatment of a disease in a mammal when a phosphodiesterase isoenzyme inhibitor and/or bronchodilator would be expected to be of benefit, which method comprises administering .... a compound of general formula I*" It is unclear if the claimed method uses only a compound of formula I, or a combination of a phospodiesterase isoenzyme (or PDE)

inhibitor, and/or a bronchodilator, **and** a compound of formula I. The claimed method seems to suggest a combined therapy of multiple agents including a compound of formula I.

b. Claims 46-48, 51 and 52 are rejected as being dependent on claim 43, and still recite the indefinite method.

c. Claim 53 recites: "*A method of treating a mammal suffering from or susceptible to a disease, disorder or condition mediated by PDE III and PDE IV isoenzyme,...*" The claimed method has indefinite metes and bounds because the specification provides and open-ended list of diseases associated with PDE isoenzymes. Note, the list of diseases has the phrase "**or any other disease including...in which increasing intracellular concentration of cAMP is considered beneficial**". Such a phrase does not set a definite metes and bounds for the claimed method. It is not clear what other diseases are intended in such a treatment. The claim language reads on diseases not yet known to be caused by or affected by such an action, or in way not yet understood. The test for determining compliance with 35 U.S.C. 112, 2nd paragragph is whether applicants have clearly defined "their" invention not what may be discovered by future research as this type of claim language clearly requires.

d. Claim 54 is rejected as being dependent on claim 53 and still recites the indefinite method.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. **Enablement (for "prophylactic treatment"):** Claims 43-48, 51 and 52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 43-45 recite a "*method for the ...**prophylactic** treatment*" which does not have enablement in terms of patient's profile, preventive dosage, onset and duration of prevention. Without such a protocol, a skilled clinician would have to carry out undue experimentation to use the claimed compound in the prevention of any intended disease. The term "prophylactic" suggests "preventing on anticipation" which is meant for preventing a pathophysiological condition that is resulted from a medical procedure (e.g., surgery), or exposure to certain environment (e.g., high elevation, or polluted area). However, a disease related to a "phosphodiesterase isoenzyme" is usually a chronic disease such as: asthma, chronic obstructive pulmonary disease (COPD), or arthritis, etc. Thus, it is unclear how a compound can prophylactically treat such a disease since the duration of said diseases is indefinite. The specification does not describe a protocol for a "prophylactic treatment" of a disease related to

"phosphodiesterase isoenzyme". Thus, the specification fails to enable a "prophylactic treatment" as recited in said claims.

3. **Scope of Enablement:** Claims 43-48 and 51-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of *allergic asthma, allergic rhinitis, hay fever, or atopic dermatitis*, does not reasonably provide enablement for the treatment of other diseases allegedly related to PDE III or PDE IV such as: *asthma, bronchitis, COPD, ARDS, cystic fibrosis, psoriasis, ocular inflammation, cerebral ischemia, or auto-immune disease in which increasing intracellular concentration of cAMP is considered beneficial.* The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors have been considered in the determination of an enabling disclosure:

(1) The breadth of the claims;

(2) The amount of direction or guidance presented;

(3) The state of the prior art;

(4) The relative skill of those in the art;

(5) The predictability or unpredictability of the art;

(6) The quantity of experimentation necessary;

[See ***Ex parte Forman***, 230 USPQ 546 (Bd. Pat. App. & Int., 1986); also ***In re Wands***, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)].

The breadth of the claims:

Claim 43 recites: "A method for the acute or prophylactic treatment of a disease where a phosphodiesterase isoenzyme inhibitor and/or bronchodilator would be expected to be of benefit..."

Said method reads on the treatment of an array of diseases as cited below:

> **[0114]** Compounds of the present invention are useful as inhibitors of phosphodiesterase isoenzymes. The compounds or compositions of the present invention may be used to prevent or treat any disease in which the compounds or compositions are useful, but particularly a disease in which raising the intracellular concentration of cAMP is desirable. Examples of diseases against which compounds are useful include respiratory disorders including, in particular, asthma, bronchitis, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), allergic asthma, hay fever, allergic rhinitis, and cystic fibrosis. They may also be used topically in skin disorders such as atopic dermatitis or psoriasis, ocular inflammation, or any other disease including cerebral ischaemia or auto-immune diseases in which increasing intracellular concentrations of cAMP is considered beneficial.

Note, the phrase "**any other disease including...in which increasing intracellular concentration cAMP is considered beneficial**" covers diseases that have yet to be discovered. Thus, the scope of claim 43 is unduly broad.

Claim 44 recites: "A method for the acute or prophylactic treatment of asthma..." which does not have an unduly broad scope, but is not enabled in terms of bioassays done.

Claim 45 recites: "A method for the acute or prophylactic treatment of chronic obstructive pulmonary disease (COPD)..." which does not have an unduly broad scope, but is not enabled in terms of bioassays done.

Claims 46-48, 51 and 52 depend on claims 43-45, and thus carry out either an unduly broad scope or non-enabled methods.

Claim 53 recites: "A method of treating a mammal suffereing form or susceptible to a disease, disorder or condition mediated by PDE III and PDE IV isoenzymes..." Like claim 43, claim 53 also covers a myriad number of diseases as cited above, and thus, its scope is unduly broad.

Claim 54 depends on claim 53, and recites specific diseases such as: *a respiratory disorder, skin disorder or auto-immune disease* **in which increasing intracellular concentration of cAMP is considered beneficial.** The term "*a respiratory disorder*" covers disorders related to the lungs, trachea, bronchioles, malignant or benign lung tumors. Likewise, "*skin disorder*" covers various forms of dermatitis, skin cancers, psoriasis, eczema, etc. Similarly, "*auto-immune disease*" encompasses just about any disease including arthritis, lupus, AIDS, etc. Thus, the scope of claim 54 is also unduly broad.

Claims 55 and 56 depend on claim 54, but recite the treatment of many disorders that are not enabled in terms of bioassays done.

Claim 57 depends on claim 53, but recite the treatment of *ocular inflammation* or *cerebral ischaemia*, which is not enabled in terms of bioassays done.

The amount of direction or guidance presented: The specification provides one *in-vitro* assay of the inhibition of PDE III and PDE IV isoenzymes, and one *in-vivo* assay of histamine induced bronchospasm. In both assays only compound of Example 1 was tested. Note, compound of Example 1 has an *unsubstituted urea* in the side chain, which does not fairly represent other compounds of formula I. The difference in the side chain could drastically alter the activity of a compound. Therefore, the activity of one compound cannot be extrapolated to other compounds where the side chain is substituted. Furthermore, there is no evidence if the claimed compound could relieve other symptoms of asthma, COPD, psoriasis, auto-immune disease, ocular inflammation, or cerebral ischemia. Thus, the specification fails to provide adequate enablement for treating many diseases related to PDE III and PDE IV using compounds of formula I.

The state of the prior art: As evident by many references cited on the IDS, the core of *3,4,6,7-tetrahydro-2H-pyrimido[6,1-a]isoquinolin-4-one* is known to treat cardiovascular disorders, particularly hypertension. No reference correlates said core to the treatment of asthma, COPD, psoriasis, ocular inflammation, cerebral ischaemia, auto-immune disease, etc. Thus, the state of the prior art does not support the method of treatment as recited in claims 43-48 and 51-57.

The relative skill of those in the art: Even with the advanced training, the skilled clinician would have to carry out extensive research to select an effective compound from the large Markush group of formula I. Not only one has to determine an IC_{50} value, but also *in-vivo* activity to establish an LD_{50}, therapeutic index and pharmacokinetic profile for **each compound**

in **each indication**. Given a large Markush group of the claimed formula I, such a task would require a tremendous amount of effort, time and resource.

The predictability or unpredictability of the art & The quantity of experimentation necessary: The pharmaceutical art has been known for its unpredictability due to various conflicting path ways, or biological factors that are sometimes genetically unique to individuals. In the instant case, the sole compound of Example 1 in two critical tests does not sufficiently enable the skilled clinician to treat the many diseases that are allegedly related to PDE III and PDE IV. See ***Hoffman v. Klaus*** 9 USPQ 2d 1657, and ***Ex parte Powers*** 220 USPQ 925 regarding type of testing needed to support *in vivo* uses.

Note, the "how to use" requirements of 35 USC 112 are not met by disclosing only a pharmacological activity of the claimed compound if one skilled in the art would not be able to use the compound effectively without undue experimentation. See **In re Diedrich**, 138 USPQ 128; **In re Gardner et. al.**, 166 USPQ 138. Thus, where claimed compounds do not bear structures that are similar to known compounds having the same activity and their pharmaceutical properties could not be predicted from their chemical structure, a disclosure that they possess a particular activity may not suffice as a description of how to use as required by 35 USC 112. See **In re Moureu et. al.** 145 USPQ 452. Note, the Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the **full scope** of the invention without 'undue experimentation'".

Thus, given the unpredictable nature of the art, and the vast number of compounds claimed herein, one skilled in the art will have to carry out undue experimentation to practice the method of treatment recited in claims 43-48 and 51-57.

No pending claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tamthom N. Truong whose telephone number is 571-272-0676. The examiner can normally be reached on M, T and Th (9:00-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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7-27-06

Tamthom N. Truong
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